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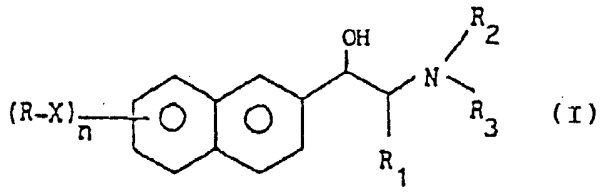
(54) Title: BICYCLIC ALKOXY- AND ALKYLTHIO-SUBSTITUTED AMINOALCOHOLS



(57) Abstract

Novel bicyclic alkoxy- and alkylthio-substituted aminoalcohols of formula (I). The compounds show anti-hypertensive, platelet aggregation inhibiting, hypolipemic, antianoxic, spasmolytic, antithrombotic, calcium antagonizing and neuroleptic activity.

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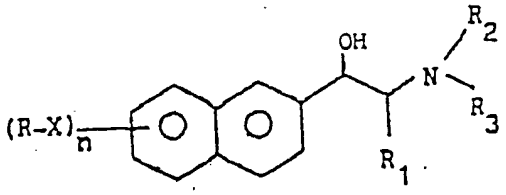
BICYCLIC ALKOXY- AND ALKYLTHIO-SUBSTITUTED AMINOALCOHOLS

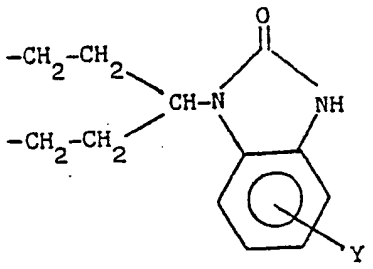
This invention is concerned with new pharmacologically active compounds. More particularly, the compounds with which this invention is concerned are bicyclic alkoxy- and alkylthio-substituted amino alcohols of the formula:



I

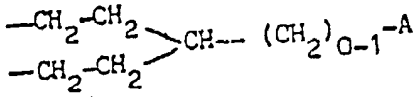
wherein R represents a lower straight or branched alkyl group, X represents -O- or -S-, n is an integer from 1 to 3, R_1 represents hydrogen or a lower alkyl group; R_2 represents hydrogen or benzyl; R_3 represents an alkyl group; or alternatively R_2 and R_3 taken together represents a divalent group selected from:

a)

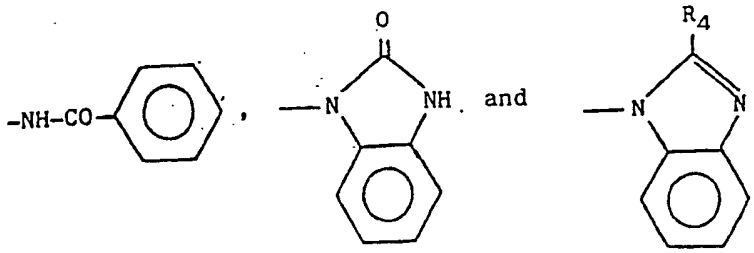


wherein Y represents hydrogen or halogen;

b)

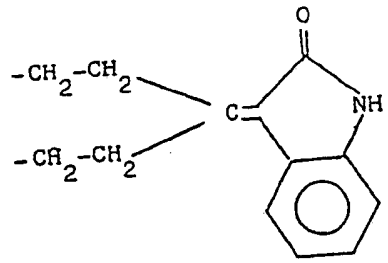


wherein A is a group selected from



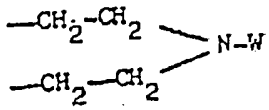
wherein R_4 represent a lower alkyl group;

c)



and

d)



wherein W represents hydrogen, phenyl, benzyl, alkoxyphenyl, methylphenyl, 2-furoyl, nicotinoyl or a radical

-CO-CH=CH-Z

in which Z represents 2-thienyl or phenyl optionally substituted with 1-3 halogen, lower alkyl or alkoxy groups: and their salts with inorganic acids, organic acids, cationic exchange resins and complexes with cyclodextrins.

As apparent to all those skilled in organic chemistry, the compounds in which R_1 does not represent hydrogen, having two structural asymmetry centers, may exist both in the erythro and threo configuration.

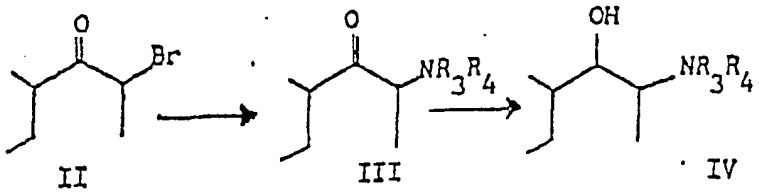
In most cases, by the manufacturing process which will be

hereinafter described, a mixture of the two steric isomers is obtained, and an appropriate separation may occasionally be necessary. In other instances, however, formation of one single isomer is so prevailing as to approach 100 per cent, and a separation is not required unless the product is desired in an analytically pure condition for purposes of study.

The configuration of the erythro and threo isomers was assigned through ^{1}H.NMR (Nuclear Magnetic Resonance) spectra by determining the characteristic coupling constants ($J_{C-1,C-2}$) of the compounds.

The chemical process for the preparation of the invention compounds consists in contacting a bromo ketone of the partial formula II with an amine to give the amino ketone of the partial formula III.

The amino ketone is then hydrogenated to give the desired amino alcohol



II III IV

Depending on the circumstances, the amino ketone III may be isolated from the reaction mixture before it is hydrogenated. On the other hand, if the intermediate III shows a low degree of stability, it is preferable to hydrogenate it directly in the reaction mixture in which it is formed by reaction of the bromo ketone with the amine.

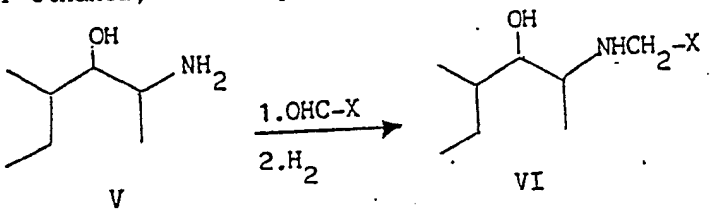
The first step of the process is carried out in the presence of a proton acceptor, such as an alkali metal or earth alkali carbonate or bicarbonate or a tertiary amine.

In some instances, an excess over the molecular amount of the same amine which is being contacted with the bromo ketone may be used with satisfactory results. Usually this first step is carried out in a solvent inert to the instant reaction such as a lower alkanol, for instance methanol or ethanol, or a ketone, such as a di-lower alkyl ketone, for instance acetone or methyl ethyl ketone. It is immaterial whether the amine is added to the bromo ketone, both or only one of them being dissolved in the solvent, or vice versa the bromo ketone is added to the amine, still both in solution or only one of them.

The appropriate way of conducting the first step will be selected considering the properties of the reactants and their reactivity. The reaction temperature is also adjusted depending on the reactivity of the two reactants, although normally the boiling temperature of the solvent is generally preferred. The second step of the process, i.e. the hydrogenation, may be carried out by any conventional hydrogenation procedures apt to convert a ketone into an alcohol. However, we have found that the hydrogenation is best performed by using a metal hydride, preferably a double hydride, such as $NaBH_4$, $LiAlH_4$ etc., by conventional procedures in a solvent inert to the hydrogenation reaction, which in the case of $NaBH_4$ may be water, or a lower alkanol, such as methanol or ethanol, both in the presence of various amounts of water of under anhydrous conditions, or alternatively, when for instance $LiAlH_4$ is used, the solvent may be diethyl ether, tetrahydrofuran and the like, at a temperature which may range from 0-5°C to the boiling temperature of the selected solvent. When the intermediate is not isolated from the reaction mixture of the first reaction step, and depending on the nature of the selected hydrogenating agent, this is added directly to the intermediate reaction mixture either in the form of a solution in an appropriate solvent not interfering with the

hydrogenation and the solution of the hydrogenating agent is added while mantaining the mixture at the reflux temperature or at a lower temperature which may be found more convenient depending on the observed reaction rate; or the hydrogenating agent may be added at portions or by dropping its solution in an appropriate solvent while maintaing the reaction mixture at a temperature ranging from 0°C to the boiling temperature of the solution until the addition is complete, then heating the mixture to reflux until the reaction is complete. Obviously the skilled chemist will select the procedure appropriate to the nature of the hydrogenating agent and the substrate and the reactant used.

An alternative process for preparing the invention compounds consists in reacting an amino alcohol of the partial formula V with an aldehyde in a solvent, preferably in a lower alkanol such as methanol or ethanol, at a temperature between about 0°C and



V VI

the reflux temperature of the solution.

To the reaction mixture a hydrogenating agent is then added at portions, the agent being preferably selected from metal hydrides or double cyano hydrides, such as sodium cyano boro hydride or lithium cyano boro hydride, these latter hydrogenating agents being preferred.

It is apparent to those having knowledge of organic chemistry that the last described method of preparation is convenient when the symbol X in the partial formula VI above represents a linear or

branched alkyl radical.

The compounds of this invention show anti-hypertensive, platelet aggregation inhibiting, hypolipemic, antianoxic, spasmolytic, antithrombotic and Ca^{++} antagonizing activity. These activities are shared both by the individual stereoisomeric forms and their mixtures, which therefore may be administered for therapeutical purposes, depending on the actuale convenience, in one or the other steric form or mixture.

The anti-hypertensive activity was tested on groups of 5 SH rats (spontaneously hypertensive rats) weighing 200±10 g, fasting for 18 hrs and treated orally with the invention compounds suspended in 2.5% gum arabic.

Changes in blood pressure (mm Hg) before (T=0) and after treatment (2, 4 and 6 hrs) were measured according to the method of tail artery plethysmography reported in "Spontaneously hypertensive rats (SHR): Guidelines for breeding, care and use", SHR Conference, 1976, page 11.

The heart rate was also tested (BP Recorder No. 8006 supplied by Basile, Comerio, Italy). The arterial pressure before the treatment was 210±10 mmHg.

Table 1 shows that the compounds are endowed with good anti-hypertensive activity at all tested doses.

The peak effect was noted 2-4 hrs after the treatment and the duration of the effect was more than 6 hrs: in this period no remarkable increase of heart rate was registered.

Administration of 5 mg/kg p.o. caused a pressure decrease higher than Tibalosine. At 1 mg/kg p.o. MG 38065 was more effective than Urapidil.

TABLE 1

COMPOUND	Max. changes in systolic pressure (mmHg) SHR 1 mg/kg p.o.		
	15	5	
MG 38065	- 41	- 43	- 34.2
MG 38095	- 47.6	- 26.5	- 18
MG 38069	- 68	- 39	- 13.6
MG 14233	- 48.2	- 31	- 14.4
Tibalosine	- 67	- 13.2	~ 0
Urapidil	- 72.4	- 47	- 16

To test the antagonism against phenylephrine (PHE) induced hypertension, male rats CrI:CD (SD)BR were anesthesized with urethane, 1 g/kg i.p.

PHE was administered cumulatively and dose-response curves were obtained (controls). Dose-response curves were similarly obtained after administration of the test drugs (1 mg/kg i.v.). From the two curves the PHE dosis causing a 50 mm Hg increase of the arterial pressure was calculated. The PHE dosis was about 9 times, in comparison with the controls, after administration of MG 38069; 20-25 times after MG 14238, MG 14233 and MG 38065; 34 times after MG 38095.

The protection against toxic adrenaline doses was tested as follows. Groups of 10-20 male mice CrI:CD 1(CR) BR were treated orally with vehicle (controls) and with various doses of the compounds. After 2 hrs 14.5 mg/kg of l-adrenaline was administered intraperitoneally and mortality was recorded after 24 hrs: in controls mortality was 100%. From log dose-% protection curves the 50% protective doses (PD_{50}) were calculated (Litchfield et al., J. Pharmacol. Exp. Ther. 96, 99, 1949).

Table 2 gives the results obtained with some of the compounds as compared with known drugs having alpha-adrenergic receptor blocking activity.

The new compounds show generally the same or higher activity as compared with Tibalosine and Phentolamine; MG 14167 and MG 14233 were comparable with Prazosin.

TABLE 2

COMPOUND	PD_{50} mg/kg/p.o.	Confidence limits (P = 0.05)
MG 14167	0.6	0.50 - 0.72
MG 38065	1.0	0.74 - 1.34
MG 38069	5.4	3.68 - 7.92
MG 38088	13.5	9.23 - 19.75
MG 14233	0.95	0.69 - 1.31
MG 38095	3.75	2.23 - 6.30
MG 14235	5.05	3.44 - 7.41
MG 14237	10.0	7.28 - 13.74
MG 14238	1.8	1.32 - 2.60
MG 14239	5.8	3.59 - 7.54
Prazosin	0.70	0.59 - 0.83
Tibalosine	5.5	3.36 - 8.99
Phentolamine	8.0	6.3 - 10.15

The receptors binding assay for the inhibition of ^{3}H-Prazosin, ^{3}H-Clonidine and ^{3}H-Spiperone binding to rat brain membrane was carried out according to Greenberg et al., Life Sci. 19, 69, 1976 and U'Prichard et al., Molec. Pharmacol. 13, 454, 1977.

Data for the tested compounds are reported in Table 3 where the 50% inhibiting concentrations (IC_{50}) of Tibalosine and Urapidil are also given. The invention compounds show a good affinity toward $alpha_1$-adrenergic receptors, comparable with or higher than the two comparison substances, and poor or no affinity toward $alpha_2$-adrenergic receptors.

A moderate affinity toward serotoninergic$_2$ ($5\text{-}HT_2$) receptors is displayed by MG 38069.

TABLE 3

COMPOUND	Concentration (M)	% Inhibition of specific binding		
		^{3}H-Prazosin (α_1)	^{3}H-Clonidine (α_2)	^{3}H-Spiperone /5-HT$_2$/
MG 38065	5.4×10^{-7}	98	0	0
	5.4×10^{-6}	100	0	38.9
MG 38069	5.4×10^{-7}	97	0	36
	5.4×10^{-6}	100	13	83
MG 38095	5.4×10^{-7}	98	0	32
	5.4×10^{-6}	100	12.5	62
MG 14167	5.4×10^{-7}	99	8	0
	5.4×10^{-6}	99	26.5	25
Tibalosine	IC_{50} (a)	4×10^{-7}	1×10^{-3}	
Urapidil	IC_{50} (b)	8×10^{-7}	1.4×10^{-5}	

a) QIAN J.H. et al. - Arch. int. Pharmacodyn 266, 264; 1983
b) VAN ZWIETEN P.A. et al. - Arch. int. Pharmacodyn. 276, 180; 1985

The effect on platelet aggregation was tested ex vivo according to the method of Minsker (J. Pharmacol. Exp. Ther. 210, 37, 1979) slightly modified. Groups of 3 rats (280-350 g) were treated orally with vehicle (controls) and compounds (0.15 mM/kg). Blood was collected and pooled from rats of each group 1 hr after treatment and the platelet rich plasma (PRP) was separated by centrifugation.

Platelet aggregation was stimulated with collagen (2-4 mcg/ml) added simultaneously to PRP of control and treated rats. The results were assessed photometrically. Each test was replicated 4 times in groups of 3 animals. Aggregation curves were evaluated in terms of two parameters namely maximum optical density variation (maximum aggregation) and aggregation rate.

Table 4 gives the effects recorded after treatment with some of the tested compounds. They show an activity comparable to Ticlopidine and Suloctidil and only slightly lower than Sulfinpyrazone.

TABLE 4

COMPOUND	% Inhibition	
	Maximum aggregation	Aggregation rate
MG 38078	70.4	64.0
MG 38068	58.8	54.4
MG 38088	68.6	75.1
MG 28472	75.7	65.3
MG 14239	64.0	64.6
Ticlopidine	70.0	56.0
Sulfinpyrazone	92.5	89.0
Suloctidil	69.0	57.5

To test the hypolipemic activity, Sprague Dawley Nos male rats (180-200 g) were treated orally for 4 consecutive days with vehicle (0.5 ml/100 g gum arabic 2.5%, controls) and with 1-3 doses of the tested compounds, and were sacrificed at the 5th day after 18 hrs fasting. Total cholesterol (CHOL), triglycerides (TG), HDL cholesterol (CHOL-HDL) were assayed in serum and the liver was weighed.

Table 5 gives the obtained results. MG 28451, MG 38065, MG 38068 and MG 28453 cause a significative decrease of serum TG and an increase of CHOL-HDL, and the other compounds are effective in decreasing both CHOL and serum TG. Among these, MG 38127 and MG 38105 exert a good activity at very low doses. The activity of the foregoing compounds is higher than with Clofibrate which, as known, causes a significative liver increase. The Probucol activity is moderate and is noted only after prolonged treatment (8 days).

Finally, in the test of ethanol induced hypertriglyceridemia (Sirtori et al. , Atherosclerosis 30, 45, 1978) the decrease of serum TG was significative and higher than 50% after administration of all mentioned compounds at doses of 0.37-0.046 mM/kg per os).

TABLE 5

COMPOUND	Dose mM/kg/p.o.	Normolipemic rats % different from control			
		CHOL	TG	CHOL-HDL	Liver Weight
MG 28451	0.37 x 4 days	- 13.5	- 48.2	+ 46.5	+ 9.2
MG 38065	0.185 " " "	+ 7.2	- 35.6	+ 11.8	- 3.6
"	0.37 " " "	- 18.1	- 49.9	+ 42.6	- 0.9
MG 38068	0.185 " " "	- 3.7	- 45.0	+ 5.0	+ 2.6
"	0.37 " " "	- 21.8	- 56.9	+ 32.9	+ 0.3
MG 38088	0.185 " " "	- 35.1	- 70.5	- 9.1	0
"	0.37 " " "	- 41.3	- 68.5	+ 5.4	+ 3.4
MG 28453	0.185 " " "	+ 8.5	- 36.4	+ 45.2	+ 2.8
"	0.37 " " "	- 26.9	- 75.4	+ 31.7	+ 21.6
MG 38127	0.023 " " "	- 30.2	- 41.4	+ 7.6	- 1.6
"	0.046 " " "	- 51.2	- 66.3	- 1.8	+ 8.6
"	0.185 " " "	- 59.1	- 81.7	- 19.8	+ 3.3
MG 38105	0.023 " " "	- 35.7	- 36.2	- 13.3	+ 5.5
"	0.046 " " "	- 45.8	- 63.8	+ 1.3	+ 8.0
"	0.185 " " "	- 96.6	- 70.6	+ 3.9	+ 4.8
MG 14244	0.37 " " "	- 42.7	- 54.4	+ 38.2	+ 8.3
Clofibrate	0.82 " " "	- 15.0	- 40.0	0	+ 19.5
Probucol	0.205 x 8 days	- 25.0	- 28.0	- 26	+ 4.0
"	0.82 x 4 days	~ 0	~0	+ 18.5	~ 0

The anti-hypoxic activity was determined according to Yasuda et al., Arch.Int. Pharmacodyn. 233, 136, 1978.

Groups of 10 male mice (21-23 g) were treated orally with vehicle (controls) and the invention compounds. After 45 or 90 minutes the animals were decapitated and the gasping time was determined. Table 6 gives the results obtained after administration of some of the invention compounds which display an activity higher than Suloctidil.

The invention compounds also showed a very low acute toxicity per os in male mice. Thus for instance, the LD_{50} was higher than 1000 mg/kg for MG 14233, MG 28451, MG 38068, MG 38088 and MG 38095, and higher than 2000 mg/kg for MG 14167, MG 14237, MG 14244, MG 38065, MG 38069 and MG 38078.

TABLE 6

COMPOUND	Dose mg/kg/p.o.	Pretreatment Time (min.)	Gasping time % diff. from control
MG 38077	100	90	+ 71.0
MG 38071	100	90	+ 32.7
MG 38088	100	45	+ 46.8
"	100	90	+ 32.2
MG 38098	100	90	+ 41.1
MG 14233	50	90	+ 52.5
"	100	90	+ 126.2
MG 14238	50	90	+ 39.3
"	100	90	+ 85.7
MG 14239	100	90	+ 61.3
Flunarizine	50	90	+ 68.7
Suloctidil	100	45	+ 27.5
	100	90	+ 11.7

It is understood also that what we claim is not limited to the compounds of formula I, but also to the intermediate ketones of formula III, inasmuch they share the valuable pharmacological properties illustrated hereinbefore.

EXAMPLE 1

erythro-2-Octylamino-1-(6-methoxy-2-naphtyl)-propanol (MG 38064)

A mixture of 4 g of 2-bromo-1-(6-methoxy-2-naphthyl)-1-propanone (13.6 mmole) (A. Marquet et al., Bull. Soc. Chim. France 90, 1962), 2.1 g of distilled n-octylamine (16.3 mmole) and 60 ml of methanol is refluxed with stirring for 6 hours. After cooling to room temperature, 1.03 g of $NaBH_4$ (27.2 mmole) are gradually added and stirring is continued for 3 hours at room temperature. The precipitate is collected, washed with water and dried.

The filtered mother liquor is cooled on ice, 18 per cent hydrochloric acid is added to precipitate additional product as the hydrochloride which is collected, recrystallized from methanol/water and converted into the free base, which is combined with the first crop.

On recristallization from methanol/water, 2.7 g of the title compound are obtained. Yield 57%; m.p. 106-108°C.

Analysis for $C_{22}H_{33}NO_2$%	calc.	C 76.92	H 9.68	N 4.08
	found	76.77	9.66	4.07

The NMR spectrum ($CDCl_3$) gave J = 4.0 Hz

EXAMPLE 2

threo-2-(N-Benzyl-N-octylamino)-1-(6-methoxy-2-naphthyl)-propanol (MG 38073).

A mixture of 11.7 g of 2-bromo-1-(6-methoxy-2-naphthyl)-1-propanone (39.9 mmole), 8 g of N-benzyl-N-octylamine (36.5 mmole) (R.E. Lutz et al, J. Org. Chem. 12, 760, 1947), 3.37 g of $NaHCO_3$ (40 mmole) and 150 ml of methanol is refluxed with stirring for 6 hours.

After this time heating to reflux is continued while 2.7 g of $NaBH_4$ (72 mmole) dissolved in 15 ml of alkaline water is gradually added.

Stirring is continued overnight at room temperature, then aqueous 18% HCl is added to acidic reaction and the solution is evaporated to dryness under reduced pressure. The residue is treated with methylene dichloride, a 5% aqueous solution of Na_2CO_3 is added to neutral reaction and the organic layer is dried and evaporated to dryness in vacuo. The residue is chromatographed through silica gel 60 Merck 70-230 mesh with petroleum ether: ethyl acetate 95:5 as the eluent. Yield 10.5 g (50%).

EXAMPLE 3

threo-2-(N-Benzyl-N-octylamino)-1-(6-methoxy-2-naphthyl)-propanol (MG 38077)

The compound of Example 2 (8.7 g) is hydrogenated at room temperature in methanol in the presence of Pd/C as the catalyst. After filtering off the catalyst the solution is evaporated to dryness under reduced pressure.

The residue is converted into the hydrochloride by the addition of hydrogen chloride in diethyl ether, then into the free base by conventional methods. Yield 4.2 g (61%); m.p. 102-103°C.

Analysis for $C_{22}H_{33}NO_2$ %	calc.	C 76.92	H 9.68	N 4.08
	found	76.74	9.65	4.09

The NMR spectrum ($CDCl_3$) gave a value of J = 8.4 Hz.

EXAMPLE 4

threo- and erythro-2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]--1-(6-methoxy-2-naphthyl)-propanol (MG 38065 and MG 38095)

A mixture of 14.84 g of 2-bromo-1-(6-methoxy-2-naphthyl)-1-propanone (50 mmole), 10 g of 4-(2-oxo-1-benzimidazolinyl)-piperidine (46 mmole), 4.25 g of $NaHCO_3$ (50 mmole) and 150 ml of methanol is refluxed with stirring for 4 hours. After cooling to room temperature, the precipitate is collected, washed with water and with diethyl ether and dried.
Yield 12.3 g (62.2%) of 2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]-1-(6-methoxy-2-naphthyl)-1-propanone (MG 38094), m.p. 216-217°C.

The foregoing ketone (10 g, 23.3 mmole) is dissolved in 200 ml of methanol, then 1.76 g of $NaBH_4$ (46.5 mmole) dissolved in 10 ml of alkaline water is dropped into the solution heated to reflux. At the end of the addition heating is continued for additional 5 hours, then the mixture is cooled to room temperature and 100 ml of water are added.

The precipitate is collected and crystallized from chloroform/diethyl ether. the threo-isomer is thus obtained.

Yield 6.8 (68%) m.p. 254-256°C. (dec.)

The filtrate is made acidic by the addition of aqueous 18% HCl and concentrated under reduced pressure. The residue is treated with ethyl acetate and made alkaline with aqueous 5% sodium carbonate. The organic layer is separated and evaporated to dryness under

reduced pressure.

The residue is purified by flash chromatography through silica gel 60 Merck 230-400 mesh, using chloroform: methanol 95:5 then 90:10 as the eluent. After crystallization from methanol, 1.5g of erythro isomer (yield 15%) are obtained, m.p. 178-180.5°C.

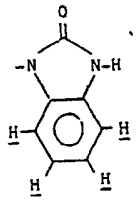
The erythro isomer was also obtained in a 55% yield by hydrogenating the intermediate propanone, MG 38094 (see above), in the presence of PtO_2 in an acetic acid-methanol mixture at 55° under a pressure of 3 atm. After purification through silicagel using chloroform:methanol 95:5 as the eluent; the erythro form was substantially pure and free from traces of the threo isomer formed during the hydrogenation.

Analysis for $C_{26}H_{29}N_3O_3$	% calc.	C 72.36	H 6.77	N 9.74
threo-isomer	found	72.21	6.76	9.72
erythro-isomer	found	72.19	6.75	9.73

The ^1H NMR spectrum (300 MHz, $CDCl_3$) gave the following values:

threo-isomer:

$delta_H$: 9.77 (1H, brs, >N-H); 7.9-7.0 (10 H, m, 6H naphthalenic and 4 H)



5.25 (1H, br, OH); 4.43 (1H,d, -CH J = 9.8 Hz);

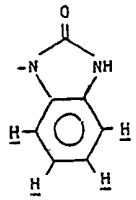
4.40 (1H, m, piperidinic); 3.93 (3H,s, OCH_3);

3.2-2.0 (7H, m, 6H piperidinic and 1H -CH-N=);

1.96 (2H, m, piperidinic); 0.84 (3H, d, $-CH_3$)

erythro-isomer

$delta_H$: 9.83 (1H, brs, >N-H); 7.9-7.0 (10H, m, 6H naphthalenic and

4H ); 5.03 (1H, d $-\underline{CH}-$ J = 4.3 Hz); 4.36 (1H, m, piperidinic); 3.92 (3H, s, OCH_3); 3.82 (1H, br, OH); 3.27 and 3.0 (2 x 1H, m, piperidinic); 2.91 (1H, m, $=\underline{CH}-N=$); 2.7-2.2 (4H, m, piperidinic); 2.0-1.7 (2H, m, piperidinic); 0.97 (3H, d, $-CH_3$).

EXAMPLE 5

threo- and erythro-2-[4-(2-Furoyl)-1-piperazinyl]-1-(6-methoxy-2--naphthyl)-propanol (MG 38066 and MG 38078).

A mixture of 6.4 g of 2-bromo-1-(6-methoxy-2-naphthyl)-1-propanone (22 mmole), 3.6 g of 1-(2-furoyl)-piperazine (20 mmole) (Althuis et al., J. Med. Chem. 20,146,1977), 1.85 g of $NaHCO_3$ (22 mmole) and 50 ml of methanol is refluxed with stirring for 6 hours. After cooling to room temperature, 1.5 g of $NaBH_4$ (40 mmole) is gradually added, then stirring is continued for additional 3 hours.

The precipitate is collected and recrystallized from chloroform/ diethyl ether. Yield 2.2 g (27.9 %) of threo isomer, m.p. 183-184°C.

From the reaction mother liquor, by addition of 18% aqueous HCl, the erythro isomer precipitates out and is collected, converted into the free base and recrystallized from acetone/hexane.

Yield 3.7 g (46.9%); m.p. 126-127°C.

Analysis for $C_{23}H_{26}N_2O_4$	% calc.	C 70.03	H 6.64	N 7.10
	threo isomer found	69.82	6.62	7.08
	erythro isomer found	69.85	6.63	7.07

The NMR spectrum ($CDCl_3$) gave:

threo isomer J = 9.8 Hz

erythro isomer J = 4.0 Hz

EXAMPLE 6

threo- and erythro-2-(4-Phenyl-1-piperazinyl)-1-(6-methoxy-2-naphthyl)-propanol (MG 38068 and MG 38088).

Prepared substantially by the process of Example 4, except that at the end of the hydrogenation the precipitate consisting of a mixture of the two diastereoisomers is separated by flash chromatography through Merck 60 silicagel 230-400 mesh, using first chloroform: acetone 95:5, then 80:20 as the eluent. After crystallization from chloroform/diethyl ether the yields are:

threo-isomer 2.3 g (50.1%); m.p. 196-198°C

erythro-isomer 1.0 g (21.8%);m.p. 188-189°C

Analysis for $C_{24}H_{28}N_2O_2$ % calc.	C 76.56	H 7.49	N 7.44
threo isomer found	76.40	7.47	7.42
erythro isomer found	76.42	7.47	7.43

The NMR spectrum ($CDCl_3$) gave:

threo-isomer J = 9.5 Hz

erythro-isomer J = 3.6 Hz

EXAMPLE 7

2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]-1-(6-methoxy-2-naphthyl)-ethanol (MG 38069)

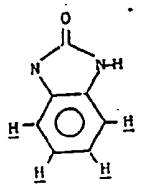
A mixture of 5.7 g of 2-bromoacetyl-6-methoxynaphthalene (20 mmole), 3.95 g of 4-(2-oxo-1-benzimidazolinyl)-piperidine (18 mmole); 1.7 g of $NaHCO_3$ (20 mmole) and 60 ml of methanol is refluxed with stirring for 5 hours, then 1.4 g of $NaBH_4$ (37 mmole) dissolved in 7 ml of alkaline water is dropped while maintaining the reaction mixture at the boiling temperature.

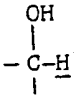
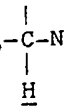
Heating is continued for additional 12 hours, then the mixture is cooled and diluted with 60 ml of water. The precipitate is collected and crystallized from methanol/water. Yield 4.5 g (59.9%); m.p. 231-233°C.

Analysis for $C_{25}H_{27}N_3O_3$ % calc. C 71.92 H 6.52 N 10.06

found 71.77 6.50 10.04

^1H NMR (300 MHz $CDCl_3$) spectrum:

$delta_H$: 9.79 (1H, br.s. >N-H); 8.0-7.0 (10H,m, 6H, naphthalenic and 4H )

4.92 (1H, d.d., ); 4.42 (1H, m, );

4.16 (1H, br, OH); 3.92 (3H, s, OCH_3); 3.41 (1H, m, piperidinic); 3.05 (1H, m, piperidinic); 2.75-2.60 (2H, m, $-CH_2-N<$); 2.60-2.30 (3H, m, piperidinic); 2.31 (1H, m, piperidinic); 2.1-1.8 (2H, m, piperidinic).

EXAMPLES 8-10

By substantially the same process as in the foregoing Example 4 and using $NaBH_4$ as the reducing agent the following compounds are prepared, with the properties and yields indicated.

2-[4-(1-Oxo-3-phenyl-2-propenyl)-1-piperazinyl]-1-(6-methoxy-2-naphthyl)-propanol.

- threo isomer (MG 38071), yield 60.8 %; m.p. 179-181°C; ^1H NMR

(300 MHz $CDCl_3$) J = 9.8 Hz

- erythro isomer (MG 38079), yield 23.4%; m.p. 172-174°C; J= 4.0 Hz

2-/4-(3-Pyridinecarbonyl)-1-piperazinyl7-1-(6-methoxy-2-naphthyl)-propanol

- threo isomer (MG 38070), yield 34.2%, m.p. 182-183°C; ^1H NMR J = 9.7 Hz

- erythro isomer, (MG 38093) yield 26%, m.p. 160-161°C; J = 4.0 Hz

2-/4-(1-Oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl)-1-piperazinyl7-1--(6-methoxy-2-naphthyl)-propanol

- threo isomer (MG 28471), yield 33%, m.p. 162.5-163.5°C

- erythro isomer (MG 28472), yield 24.1%, m.p. 165.5-166.5°C.

The elemental analysis and the NMR spectra confirmed the structure of all the six above mentioned compounds.

EXAMPLE 11

threo- and erythro-2-/4-(2-Furoyl)-1-piperazinyl7-1-(6-methylthio--2-naphthyl)-propanol (MG 28446 and MG 28451)

To 50 g of 6-methylthio-2-naphthyl ethyl ketone (0.217 mole) (NG. Buu Hoi et al., J. Chem. Soc. 485, 1953) in 270 ml of anhydrous tetrahydrofuran, 81.61 g of phenyl trimethyl ammonium tribromide (0.217 mole) are added at portions during 5 hours with stirring at room temperature.

The mixture is stirred overnight, then it is poured into ice water containing 10% of $NaHCO_3$ and extracted with diethyl ether. The organic layer is washed with an aqueous 5% solution of $Na_2S_2O_3$, dried over Na_2SO_4 and evaporated to dryness. The residue is recrystallized from isopropanol. Yield 62 g (92.2%) of 6-methylthio-2--naphthyl alpha-bromomethyl ketone, m.p. 118-119°C.

A mixture of 22.65 g of the foregoing ketone (66.5 mmole), 12 g of 1-(2-furoyl)-piperazine (66.5 mmole), 6.15 g of $NaHCO_3$ (73.2 mmole) and 120 ml of methanol is refluxed with stirring for one night. The mixture is then cooled and 5.03 g of $NaBH_4$ (133 mmole) is gradually added at 0-5°C. After one night at room temperature, to the mixture cooled at 0-5°C 100 ml of water is added and the precipitate is collected and purified by flash chromatography through silicagel Merck 60 230-400 mesh, with ethyl acetate: light petroleum 85:15 as the eluent.

Yield: threo-isomer 8.6 g (31.5 %), m.p. 167-168°C;
erythro-isomer : 8.9 g (32.6 %), m.p. 144.5-145.5°C.

Analysis for $C_{23}H_{26}N_2O_3S$ %	calc.	C	67.28	H 6.38	N 6.82
	threo-isomer, found		67.14	6.39	6.80
	erythro-isomer, found		67.18	6.37	6.80

The NMR spectrum gave J = 9.7 Hz for the threo-isomer and J=3.7 Hz for the erythro-isomer.

EXAMPLES 12-18

Starting from 6-methyltio-2-naphthyl alpha-bromomethyl ketone (see Example 11) and reacting it with the appropriate amine by substantially the same process as the one used above for the preparation of the compound of Example 11, the following compounds are prepared, of which the yields and the melting points are reported. The elemental analysis and the NMR spectra confirmed the structure and the stereoisomeric form of all compounds.

EXAMPLE 12

2-[4-(1-Oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl)-1-piperazinyl]-1-(6-methylthio-2-naphthyl)-propanol

threo-isomer (MG 28447) : 40.8%; m.p. 197.5-199°C. J = 9.7 Hz

erythro-isomer (MG 28452) : 34.3%; m.p. 172-172.5°C. J = 3.7 Hz.

EXAMPLE 13

2-[4-(3-Pyridinylcarbonyl)-1-piperazinyl]-1-(6-methylthio-2-naphthyl)-propanol.

threo-isomer (MG 28453) : 34.8%; m.p. 159.5-160.5°C. J = 9.5 Hz

erythro-isomer (MG 28473) : 25%; m.p. 110-111°C. J = 4 Hz

EXAMPLE 14

threo-2-(4-Phenyl-1-piperazinyl)-1-(6-methylthio-2-naphthyl)-propanol (MG 28428) : 64%; m.p. 239.5-240.5°C. J = 9.9 Hz.

EXAMPLE 15

threo-2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]-1-(6-methylthio-2-naphthyl)-propanol (MG 14167) : 59.6%; m.p. 277-278°C. J = 9 Hz.

EXAMPLE 16

2-[4-(1-Oxo-3-(2-thienyl)-2-propenyl)-1-piperazinyl]-1-(6-methylthio-2-naphthyl)-propanol.

threo-isomer (MG 14168) : 39%; m.p. 177.5-178.5°C. J = 9.8 Hz.

erythro-isomer (MG 14187) : 24%; m.p. 153-155°C. J = 4 Hz.

EXAMPLE 17

erythro-2-Octylamino-1-(6-methylthio-2-naphthyl)-propanol (MG 28280): 51%; m.p. 95-95.5°C. J = 3.8 Hz

EXAMPLE 18

2-[4-(1-Oxo-3-phenyl-2-propenyl)-1-piperazinyl]-1-(6-methylthio-2-naphthyl)-propanol.

threo-isomer (MG 28295) : 32.1%; m.p. 180-181°C. J = 8 Hz.

erythro-isomer (MG 28353) : 25.4 %; m.p. 158.5-160°C. J = 4 Hz.

EXAMPLE 19

threo-2-/4-(2-Methoxyphenyl)-1-piperazinyl7-1-(6-methoxy-2-naphthyl)-propanol (MG 38098).

Preparation according to Example 1 from the same bromoketone and 1-(2-methoxyphenyl)-piperazine through 2-/4-(2-methoxyphenyl)-1-piperazinyl7-1-(6-naphthyl)-1-propanol (MG 38096); this intermediate has m.p. 106-107°C, yield 85%.

Yield of the end compound 59%; m.p. 206-208°C. J = 9.5 Hz

EXAMPLE 20

2-(4-Benzamido-1-piperidinyl)-1-(6-methoxy-2-naphthyl)-propanol

Prepared according to Example 4 from the same propanone and 4-benzamidopiperidine. The intermediate amino ketone (MG 38141) has m.p. 175-177°C and is reduced using $NaBH_4$ as the reducing agent.

threo-isomer (MG 38105) : 26.6%; m.p. 237-239°C J = 9.8 Hz

erythro-isomer (MG 38127) : 24,4%; m.p. 189-191°C J = 4.0 Hz

EXAMPLE 21

threo-2-/4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl7-1-(6,7-dimethoxy-2-naphthyl)-propanol (MG 14233).

From 1-(6,7-dimethoxy-2-naphthyl)-1-propanone and phenyl trimethyl ammonium tribromide through 2-bromo-1-(6,7-dimethoxy-2-naphthyl)-1-propanone (yield 84%; m.p. 122-124°C) which is then reacted with 4-(2-oxo-1-benzimidazolinyl)-1-piperidine followed by reduction with $LiAlH_4$. Yield 55%; m.p. 246-248°C. J = 9.5 Hz.

EXAMPLE 22

2-/4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl7-1-(6,7-dimethoxy-2-

naphthyl)-ethanol (MG 14235)

From 1-(6,7-dimethoxy-2-naphthyl)-1-ethanone and phenyl trimethyl ammonium tribromide. The intermediate bromoketone (MG 14228; yield 65%; m.p. 136-137.5°C) is reacted with 4-(2-Oxo-1-benzimidazolinyl)-1-piperidine followed by reduction with $LiAlH_4$ in tetrahydrofuran. Yield 60%; m.p. 205-207°C.

EXAMPLE 23

threo-2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]-1-(6-isopropoxy-2-naphtyl)-propanol (MG 14238)

6-Propionyl-2-naphthol and 2-iodopropane give 1-(6-isopropoxy-2-naphthyl)-1-propanone (m.p. 79-80°C) which is converted into the bromo derivative (MG 14226), m.p. 82-83°C. This compound is processed as in the preceding Example. Yield 52%; m.p. 254-256°C. J = 9.8 Hz.

EXAMPLE 24

2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]-1-(6-isopropoxy-2-naphthyl)-ethanol (MG 14237)

Prepared as in Example 23 starting from 6-acetyl-2-naphthol through the corresponding ethanone (MG 14222 m.p. 54-56°C).
The intermediate bromo ketone (MG 14224) has m.p. 91-93°C.
The end compound (MG 14237) has m.p. 217-219°C.

EXAMPLE 25

2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]-1-(6-methoxy-2-naphthyl)-1-butanol.

From 2-bromo-1-(6-methoxy-2-naphthyl)-1-butanone and 4-(2-Oxo-1-

-benzimidazolinyl)-1-piperidine and reduction of the intermediate butanone (m.p. 177-178°C) with $NaBH_4$. The steric isomers are separated as the hydrochlorides by crystallization from methanol.

threo-isomer (MG 14242) : 60%; m.p. 218-220°C. J = 9.5 Hz

erythro-isomer (MG 14247) : 20%; m.p. 197-198°C. J = 4.7 Hz

EXAMPLE 26

2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]-1-(6-methoxy-2-naphthyl)-pentanol.

From 1-(6-methoxy-2-naphthyl)-1-pentanone through the 2-bromo derivative (m.p. 78-80°C) which is processed as in the foregoing Examples.

threo-isomer (MG 14250) : 60%; m.p. 228-230°C (hydrochloride).

J = 9.5 Hz.

erythro-isomer (MG 14251) : 15%; m.p. 140-141°C (hydrochloride).

J = 4.0. Hz.

EXAMPLE 27

threo-2-[4-(2-Oxo-5-chloro-1-benzimidazolinyl)-1-piperidinyl]-1-(6-methoxy-2-naphthyl)-propanol (MG 14239).

Prepared as in the preceding Example from 4-(2-oxo-5-chloro-1-benzimidazolinyl)-piperidine. Yield 60%; m.p. 274-276°C (dec.).

J = 9.8 Hz.

EXAMPLE 28

2-[4-(2-Methyl-1-benzimidazolinyl)-1-piperidinyl]-1-(6-methoxy-2-naphthyl)-propanol.

Prepared as in the preceding Example from 4-(2-methyl-1-benzimidazolinyl)-1-piperidine.

threo-isomer (MG 14249) : 52%; m.p. 165-167°C. J = 9.6 Hz.

erythro-isomer (MG 14254) : 20%; m.p. 159-161°C. J = 4 Hz.

EXAMPLE 29

2-/4-(2-Oxo-1-benzimidazolinyl)-methyl-1-piperidinyl/-1-(6-methoxy-2-napthyl)-propanol.

threo-isomer (MG 14263). 69%; m.p. 221-223°C. J = 9.5 Hz.

erythro-isomer (MG 14265). 15%; m.p. 177-179°C. J = 4.0 Hz.

EXAMPLE 30

2-/4-(2-Oxo-3-indolinylidene)-1-piperidinyl/-1-(6-methoxy-2-naphthyl)-propanol.

threo-isomer (MG 14264): J = 9.6 Hz.

erythro-isomer (MG 14266): J = 4.0 Hz.

EXAMPLE 31

2-(1-Piperazinyl)-1-(6-methoxy-2-napthyl)-propanol.

From 2-bromo-1-(6-methoxy-2-naphtyl)-1-propanone and 1-benzylpiperazine, the compound 2-(4-benzyl-1-piperazinyl)-1-(6-methoxy-2-naphtyl)-1-propanone is prepared (MG 14256; m.p. 89-91°C, which is reduced with $NaBH_4$ to the corresponding amino alcohol as a mixture of the two stereoisomeric forms which are separated by flash chromatography.

threo-isomer, (MG 14259), Yield 54%, m.p. 149-150°C, J = 9.8. Hz.

erythro-isomer, (MG 14260), Yield 24%, m.p. 172-174°C, J = 4 Hz.

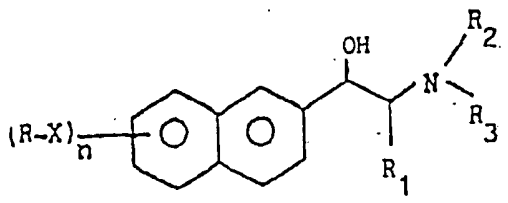
There are debenzylated by hydrogenation in the presence of Pd/C as the catalyst.

threo-isomer (MG 14258), Yield 84%, m.p. 164-166°C. J = 10 Hz.

erythro-isomer, (MG 14262), Yield 63%, m.p. 208-212°C, J = 4 Hz.

CLAIMS:

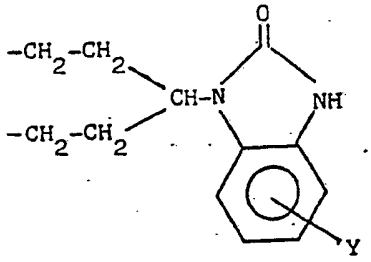
1) A compound of the formula



I

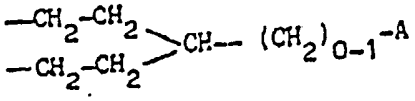
wherein R represents a lower straight or branched alkyl group, X represents -O- or -S-, n is an integer from 1 to 3, R_1 represents hydrogen or a lower alkyl group; R_2 represents hydrogen or benzyl; R_3 represents an alkyl group; or alternatively R_2 and R_3 taken together represent a divalent group selected from:

a)

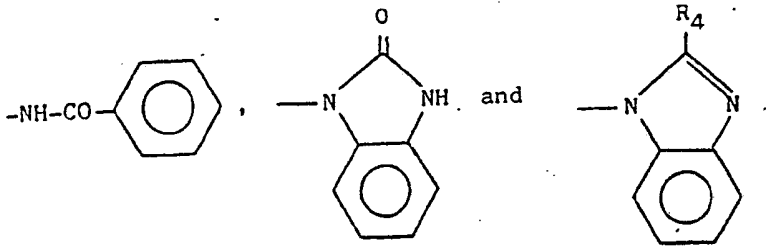


wherein Y represents hydrogen or halogen;

b)

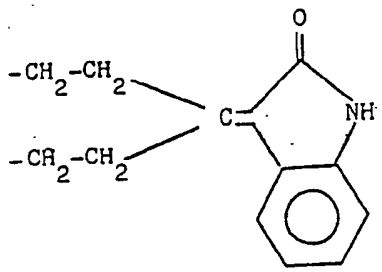


wherein A is a group selected from



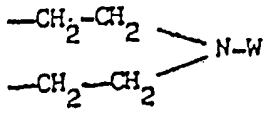
wherein R_4 represent a lower alkyl group;

c)



and

d)



wherein W represents hydrogen, phenyl, benzyl, alkoxyphenyl, methylphenyl, 2-furoyl, nicotinoyl or a radical

$$-CO-CH=CH-Z$$

in which Z represents 2-thienyl or phenyl optionally substituted with 1-3 halogen, lower alkyl or alkoxy groups: and its salts with inorganic acids, organic acids, cationic exchange resins and complexes with cyclodextrins.

2) A compound selected from the stereoisomeric threo and erythro form of 2-/4-(2-oxo-1-benzimidazolinyl)-1-piperidinyl/-1-(6--methoxy-2-naphthyl)-propanol.

3) A compound selected from the stereoisomeric threo and erythro form of 2-/4-(2-furoyl)-1-piperazinyl/-1-(6-methoxy-2-naphtyl)-propanol.

4) A compound selected from the stereoisomeric threo and erythro form of 2-(4-phenyl-1-piperazinyl)-1-(6-methoxy-2-naphthyl)--propanol.

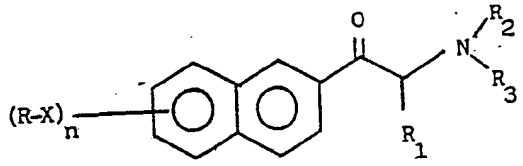
5) 2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]-1-(6-methoxy-2--naphthyl)ethanol.

6) A compound selected from the stereoisomeric threo and erythro form of 2-(4-benzamido-1-piperidinyl)-1-(6-methoxy-2-naphthyl)--propanol.

7) A compound selected from the stereoisomeric threo and erythro form of 2-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]-1-(6,7-dimethoxy-2- naphtyl)-propanol.

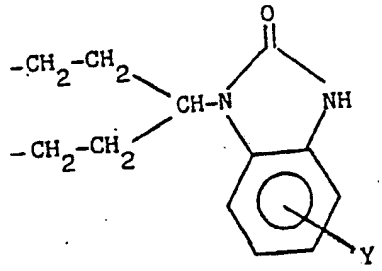
8) A compound selected from the stereoisomeric threo and erythro form of 2-[4-(1-oxo-3-(3,4,5-trimethoxyphenyl-2-propenyl)-1-piperazinyl]-1-(6-methylthio-2-naphthyl)-propanol.

9) A compound of the formula



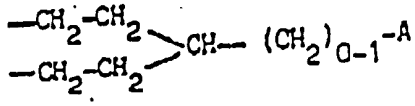
wherein R represents a lower straight or branched alkyl group, X represents -O- or -S-, n is an integer from 1 to 3, R_1 represents hydrogen or a lower alkyl group; R_2 represents hydrogen or benzyl; R_3 represents an alkyl group; or alternatively R_2 and R_3 taken together represents a divalent group selected from:

a)

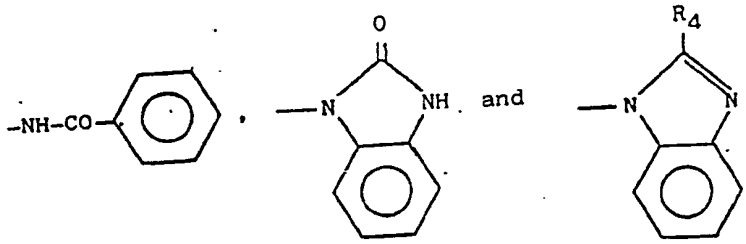


wherein Y represents hydrogen or halogen;

b)

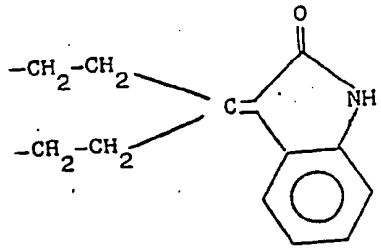


wherein A is a group selected from



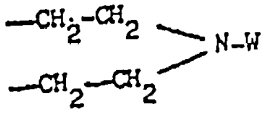
wherein R_4 represent a lower alkyl group;

c)



and

d)

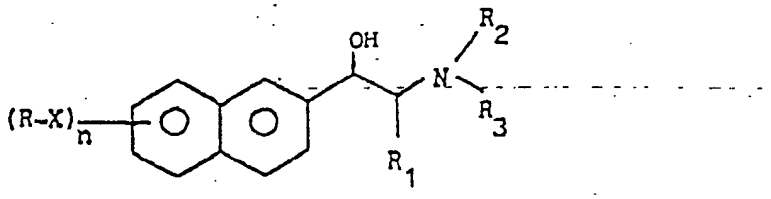


wherein W represents hydrogen, phenyl, benzyl, alkoxyphenyl, methylphenyl, 2-furoyl, nicotinoyl or a radical

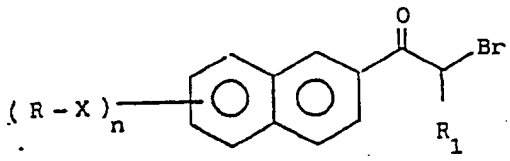
-CO-CH=CH-Z

in which Z represents 2-thienyl or phenyl optionally substituted with 1-3 halogen, lower alkyl or alkoxy groups.

10) A process for preparing a compound of the formula



which comprises contacting an alpha-haloketone of the formula



with a secondary amine of the formula HNR_2R_3 wherein R, R_1, R_2, R_3 X and n have the significance indicated in claim 1, in the presence of a proton acceptor and optionally in the presence of an inert solvent, and hydrogenating the obtained aminoketone with a reducing agent selected from a metal hydride, a double metal hydride, hydrogen in the presence of a catalyst.

PCT

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A3

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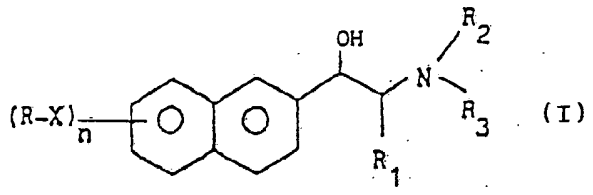

(57) Abstract

Novel bicyclic alkoxy- and alkylthio-substituted aminoalcohols of formula (I). The compounds show anti-hypertensive, platelet aggregation inhibiting, hypolipemic, antianoxic, spasmolytic, antithrombotic, calcium antagonizing and neuroleptic activity.

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INTERNATIONAL SEARCH REPORT

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I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

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IPC[4]: C 07 D 235/26; C 07 D 235/22; C 07 C 93/14; C 07 D 307/68; C 07 D 295/08; C 07 D 213/80; C 07 D 333/22; C 07 C 149/42;

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II. FIELDS SEARCHED

Minimum Documentation Searched [7]

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III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0092391 (KYOWA) 26 October 1983 --	
A	EP, A, 0076530 (JANSSEN) 13 April 1983 --	
A	Chemical Abstracts, volume 103, no. 15, 14 October 1985, (Columbus, Ohio, US), see page 698, abstract 123196w, & JP, A, 60100542 (OTSUKA PHARMACEUTICAL FACTORY, INC.) 4 June 1985	

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29th June 1987	27 JUL 1987
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

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Classification System	Classification Symbols
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INTERNATIONAL APPLICATION NO. PCT/EP 86/00595 (SA 14909)

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EP-A- 0092391	26/10/83	JP-A-	58180481	21/10/83
EP-A- 0076530	13/04/83	AU-A-	8892582	14/04/83
		CA-A-	1183847	12/03/85
		AU-B-	553845	31/07/86